REMARKS

In the Office Action mailed July 7, 2003, the Examiner rejected claims 1, 4-6, and 9-11 under 35 U.S.C. 103(a) as being unpatentable over Nasir et al., *Combinatorial Chemistry & High Throughput Screening* ("Nasir") in view of Pestka et al., *Food Technology* ("Pestka"), rejected claims 2 and 7 under 35 U.S.C. 103(a) as being unpatentable over Nasir, in view of Pestka, and further in view of Michel et al., U.S. Patent No. 5,741,654 ("Michel"), and rejected claims 3 and 8 under 35 U.S.C. 103(a) as being unpatentable over Nasir, in view of Dixon, and in further view of McMahon et al., U.S. Patent No. 5,166,078 ("McMahon").

Applicants thank the Examiner for the opportunity to discuss claim 1 and the Nasir and Pestka references during the telephonic interview conducted on October 7, 2003. During the interview, Applicants' representative argued that claim 1 was patentable over Nasir in view of Pestka because these references do not teach what tracer or antibody to use in a fluorescence polarization assay that is able to detect DON or other trichothecenes in grains. The outcome of that interview was that Applicants' representative agreed to submit evidence of non-obviousness with a Request for Continued Examination (RCE).

For the reasons set forth below, Applicants traverse the claim rejections and request reconsideration.

I. Claim Rejections

A. The Examiner Has Not Made A *Prima Facie* Case of Obviousness

With respect to the Examiner's rejections of the claims under § 103, Applicants submit that the Examiner has not established a *prima facie* case of obviousness, for the reasons set forth in Applicants' previously-filed "Response to Office Action Mailed October 17, 2002."

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However, rather than repeat those arguments in their entirety, Applicants focus on the Examiner's improper "obvious to try" rationale. In particular, it is clearly improper for the Examiner to argue that a claimed invention is obvious when the prior art gives only general guidance as to the form of the claimed invention or how to achieve it:

> In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. ... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

See MPEP § 2145(X)(B).

However, that is precisely what the Examiner is arguing in this case. Specifically, the Examiner argues that Nasir and Pestka render the pending claims obvious, even though these references do not teach what tracer to use or what antibody to use in order to achieve a fluorescence polarization assay that is able to detect DON or other trichothecenes in grains. With respect to the Nasir reference, the Examiner has conceded that Nasir does not refer to deoxynivalenol (DON) or other trichothecenes specifically. Thus, the Nasir reference fails to teach what tracer to use or what antibody to use in a fluorescence polarization assay for DON or other trichothecenes. With respect to the Pestka reference, Pestka does not mention the fluorescence polarization technique at all. To the contrary, Pestka teaches using RIA and ELISA techniques to detect DON and other trichothecenes. Thus, the Pestka reference also fails to teach what tracer to use or what antibody to use in a fluorescence polarization assay for DON or other trichothecenes. Accordingly, the Examiner has not made a proper *prima facie* case of obviousness.

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B. Evidence of Non-Obviousness

Even assuming that the Examiner has somehow made a proper *prima facie* case of obviousness, Applicants present herein substantial evidence of non-obviousness.

Because the Examiner has not identified any prior art teaching of what specific tracer or antibody to use in a fluorescence polarization assay for DON or other trichothecenes, the Examiner is apparently assuming that the level of ordinary skill in the art is such that the selection of a suitable tracer and antibody would have been obvious. The Examiner has not provided any support for this view. However, ascertaining the capabilities of one of ordinary skill in the art is crucial:

> The examiner must ascertain what would have been obvious to one of ordinary skill in the art at the time the invention was made, and not to the inventor, a judge, a layman, those skilled in remote arts, or to geniuses in the art at hand.

See MPEP 2141.03.

The evidence presented herein shows that, even for the experts in the field, the selection of suitable tracers and antibodies for fluorescence polarization assays is an active area of research, not simply a routine exercise. For example, a recent article regarding fluorescence polarization assays for pesticides from one of the experts in the field points out some of the difficulties of developing fluorescence polarization assays:

> Some attempts to develop FPIAs using antibodies from ELISA have failed, for example for p-nitrophenol, dioxins, and some organophosphates.... The FPIA is a competitive immunoassay method and this may have particular significance for antibodies against very small or highly hydrophobic pesticides. As a result, *the development of suitable antibodies and the design of fluorescein-labeled tracers for the FPIA of pesticides remain objectives for research.*

Sergei A. Eremin and David S. Smith, "Fluorescence Polarization Immunoassays for Pesticides," *Combinatorial Chemistry & High Throughput Screening*, vol. 6, p. 263 (2003)(emphasis added);

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Jolley Decl., ¶ 10. The article also points out that, while fluorescence polarization assays have a number of advantages, they also have a number of disadvantages, including sensitivity to interference from the sample, non-specific binding of the tracer with components in the sample, and the fact that, in general, labeling can affect antibody binding. Eremin, pp. 259-260.

The principles underlying fluorescence polarization assays are well established. Jolley Decl., ¶ 5. Increasing the effective molecular size of a fluorescently labeled antigen, e.g., by antibody binding, can often be detected as an increase in fluorescence polarization. Jolley Decl., ¶ 6. However, it is not the case that the binding of any fluorescently labeled antigen with an antibody will necessarily produce a detectable change in fluorescence polarization. Jolley Decl., ¶ 7. In practice, sometimes the binding can be detected as a change in fluorescence polarization; sometimes it cannot. Jolley Decl., ¶ 7. For example, the "propeller effect" can prevent any change in fluorescence polarization from being observed. Jolley Decl., ¶ 8. Labeling the antigen to form the fluorescent tracer can also interfere with its ability to bind with the corresponding antibody. Jolley Decl., ¶ 9.

In fact, the inventors encountered such difficulties when trying to develop a fluorescence polarization assay for DON. Three monoclonal antibodies that had been developed for ELISA were tried in a fluorescence polarization for DON. However, in these experiments, which used fluoresceinamine isomer II as the fluorophore, only two of these antibodies worked. Unexpectedly, the antibody that was most sensitive in the ELISA format did not work in the fluorescence polarization format, apparently, because it did not bind to the tracer or because it bound to the tracer without producing a detectable change in fluorescence polarization:

> Three murine monoclonal antibodies developed previously for ELISA applications were tested ... Two of these, produced by reference clones 1 and 4, were capable of interacting with the tracer and increasing the polarization signal

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> while the third antibody (#22) did not. Apparently, antibody 22, which was the most sensitive antibody in the competitive direct ELISA format, either did not bind the tracer or did not affect the polarization of the tracer. Although the remaining two clones were less sensitive in the ELISA format, they nevertheless were very sensitive in the FP immunoassay format.

C.M. Maragos, M.E. Jolley, and M.S. Nasir, "Flourescence polarization as a tool for the determination of deoxynivalenol in wheat," *Food Additives and Contaminants*, vol. 19, p. 403 (2002); Jolley Decl., ¶ 11. In later work, it was found that antibody #22 could be used in a fluorescence polarization assay for DON by using 4'-(aminomethyl) fluorescein instead of fluoresceinamine isomer II. Chris M. Maragos and Ronald D. Plattner, "Rapid Fluorescence Polarization Immunoassay for the Mycotoxin Deoxynivalenol in Wheat," *J. Agric. Food Chem.*, vol. 50, p. 1829 (2002); Jolley Decl., ¶ 12.

The history of these attempts to develop fluorescence polarization assays for DON show that predicting the performance of a particular tracer or antibody in a fluorescence polarization assay is *not* within the level of ordinary skill of the art. To the contrary, the development of suitable tracers and antibodies for fluorescence polarization is an active area of research, and successful results constitute publishable material.

Moreover, the fact that antibody #22 did not work when using fluoresceinamine isomer II is powerful evidence of the non-obviousness of selecting a suitable tracer and antibody:

> Absence of property which a claimed invention would have been expected to possess based on the teaching of the prior art is evidence of unobviousness.

See MPEP § 716.02(a). In this case, the Examiner relies on the Pestka reference, which teaches using ELISA to detect DON. Thus, under the Examiner's obviousness rationale, one would expect antibody #22, which was the most sensitive in the ELISA format, to work in the

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fluorescence polarization format. The fact that antibody #22 did not work with fluoresceinamine isomer II, then, is important evidence of the non-obviousness of the claimed invention.

Accordingly, Applicants submit that claims 1, 5, and 10, which recite a tracer with the special property of being able to bind to the antibody to produce a detectable change in fluorescence polarization, are allowable over the prior art of record, including Nasir and Pestka. Applicants further submit that claims 2-4, 6-9 and 11 are also allowable as depending from allowable claims.

II. Information Disclosure Statement

In the Office Action mailed July 7, 2003, the Examiner stated that an Information Disclosure Statement allegedly filed January 6, 2003 was non-compliant. During the October 7, 2003 interview, Applicants' representative stated that no Information Disclosure Statement for this application had been filed on January 6, 2003. The Examiner acknowledged that the statement made in the Office Action was actually directed to an Information Disclosure Statement that belonged to a different application but was mistakenly placed in the file for this application. Applicants thank the Examiner for this clarification.

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CONCLUSION

Applicants submit that the present application is now in condition for allowance and notice to that effect is hereby requested. Should the Examiner feel that further dialog would advance the subject application to issuance, the Examiner is invited to telephone the undersigned at any time at (312) 913-0001.

Respectfully submitted,
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